NOVARTIS

Lamisil®

Composition

Active substances: terbinafine, as terbinafine hydrochloride.

Excipients:
125 mg: magnesium stearate; hydroxypropylmethyl cellulose; microcrystalline cellulose; lactose; sodium carboxymethyl starch.
250 mg: magnesium stearate; silica colloidal anhydrous; hydroxypropylmethyl cellulose; microcrystalline cellulose; sodium carboxymethyl starch.
Pharmaceutical form and quantity of active substance per unit
Scored tablets of 125 mg (for paediatric use) and 250 mg.

Indications/Potential uses

- Onychomycosis (fungal infection of the nail) caused by dermatophytes (filamentous fungi).
- Fungal infections of the skin and hair caused by dermatophytes such as Trichophyton spp. (e.g. *T. rubrum, T. mentagrophytes, T. verrucosum, T. tonsurans, T. violaceum*), *Microsporum canis* and *Epidermophyton floccosum*.

Oral Lamisil should only be used to treat extensive severe dermatophyte infections (tinea corporis, tinea cruris, tinea pedis and tinea capitis) and yeast infections of the skin caused by the genus Candida (e.g. *Candida albicans*) where oral therapy is considered necessary owing to the site, severity or extent of the infection.
Oral Lamisil is not effective against vaginal candidiasis or pityriasis (tinea) versicolor.

Dosage/Administration

The duration of treatment varies according to the indication and the severity of the infection.
Care should be taken to ensure that treatment is given for an adequate length of time. Inadequate treatment duration and/or irregular use of the product may result in recurrence of infection.
The tablets are taken orally with water, preferably at the same time each day. They may be taken with or without food.

Usual dosage
Adults: 250 mg once daily.

Duration of treatment
Tinea corporis, t. cruris: 2-4 weeks.
Tinea capitis: 4 weeks.
Tinea pedis (interdigital, plantar/moccasin type): 2-6 weeks.
Cutaneous candidiasis: 2-4 weeks.
Onychomycosis caused by dermatophytes: 6-12 weeks.
Treatment for longer periods may be necessary in patients with slow nail growth.
Fingernail infection: 6 weeks of treatment are sufficient in most cases.
Toenail infection: 12 weeks of treatment are sufficient in most cases.
In patients with fungal infections of the nails clinical cure is often seen some months after mycological cure. This is related to the period required for outgrowth of healthy nail.

Procedure if a dose is forgotten
If a patient forgets a dose, the forgotten dose should be taken as soon as the patient realises. However, owing to the pharmacokinetic properties of terbinafine, the forgotten dose should not be taken if the next dose is already due in less than 4 hours.

Special dosage instructions
Paediatric patients
Adolescents weighing >40 kg (normally aged >12 years): 250 mg once daily.
Children weighing 20-40 kg (normally aged 5-12 years): 125 mg once daily.
Children weighing <20 kg (normally aged <5 years): data from controlled studies in this patient population are very limited and the drug should therefore be used only if there is no therapeutic alternative and the potential benefits outweigh the possible risks.
Due to the lack of data on oral Lamisil in children under 2 years of age its use in such patients cannot be recommended.

Elderly patients
There is no evidence to suggest that elderly patients require a different dosage than that used in younger patients. The possibility of existing hepatic or renal impairment should be considered in this age group (see "Renal impairment").

Renal impairment
Lamisil tablets have not been adequately studied in patients with renal impairment and therefore not recommended in this population (see "Warnings and precautions" and "Pharmacokinetics").

Hepatic impairment
Lamisil tablets are contraindicated in patients with acute or chronic liver disease (see "Warnings and precautions" and "Pharmacokinetics").

General
Good general hygiene is necessary in order to prevent reinfection (from underwear, socks, shoes, etc.).

Contraindications

- Acute or chronic liver disease.
- Known hypersensitivity to terbinafine or any of the excipients of Lamisil tablets.

Warnings and precautions

Oral Lamisil should only be used in cases that cannot be treated topically.
Use in children weighing less than 20 kg is not recommended (see "Dosage/Administration").

Liver function
Use of Lamisil tablets is contraindicated in patients with acute and chronic liver disease.
In patients with existing liver disease terbinafine clearance may be reduced by about 50% (see "Pharmacokinetics").
Patients must be examined for existing liver disease prior to the start of treatment with Lamisil tablets. As a minimum, AST and ALT should be determined so that the baseline values are available for comparison when checks are performed during therapy.
Hepatotoxicity may occur in patients with or without existing liver disease. Therefore, periodic monitoring (every 4-6 weeks) of liver function values is recommended. If liver function values increase, Lamisil must be immediately discontinued.
Very rare cases of serious hepatic failure (some with a fatal outcome or requiring liver transplantation) have been reported in patients treated with Lamisil tablets. The majority of these patients had serious underlying systemic conditions (see "Contraindications" and "Adverse effects").
Patients who are prescribed Lamisil tablets should be instructed to inform their doctor immediately of symptoms such as persistent nausea, loss of appetite, fatigue, vomiting, pain in the upper right abdomen, jaundice, dark urine or pale stools. Patients with such symptoms should stop taking oral terbinafine and their liver function should be evaluated immediately.

Renal function
Lamisil tablets have not been adequately studied in patients with renal impairment (creatinine clearance <50 ml/minute or serum creatinine >300 µmol/litre). Lamisil is therefore not recommended in such patients (see "Pharmacokinetics").

Hypersensitivity reactions/serious skin reactions
There have been very rare reports of serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms [DRESS syndrome]) in patients taking Lamisil tablets. As well as skin reactions and eosinophilia DRESS syndrome may involve one or more of the following: organ effects: hepatitis, interstitial nephritis, interstitial pneumonitis, myocarditis, pericarditis. If progressive skin rash or other symptoms of possible hypersensitivity occur, treatment with Lamisil tablets should be discontinued.

Lupus erythematosus/psoriasis
Terbinafine should be used with caution in patients with pre-existing psoriasis or (cutaneous or systemic) lupus erythematosus, as precipitation and exacerbation of these illnesses have been reported in the post-marketing setting.

Haematological effects
Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with Lamisil tablets. The aetiology of these blood dyscrasias should be evaluated and a possible change in the terbinafine dosage – including interruption of treatment with Lamisil tablets – should be considered.

Interactions
In vitro and *in vivo* studies have shown that terbinafine inhibits the hepatic enzyme CYP2D6. Patients should be monitored accordingly if they are receiving concomitant treatment with drugs predominantly metabolised by CYP2D6 (e.g. tricyclic antidepressants, beta blockers, selective serotonin reuptake inhibitors, class 1A, 1B and 1C antiarrhythmics or type-B MAO inhibitors), especially if these medicinal products have a narrow therapeutic window (see "Interactions").
Lamisil 125 mg tablets contain lactose (21 mg/tablet). Patients with rare hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Lamisil 125 mg tablets.

Interactions

Influence of other medicinal products on terbinafine pharmacokinetics
Terbinafine metabolism involves cytochrome P450 isoenzymes (CYP450) (see "Pharmacokinetics"). Plasma clearance of terbinafine may therefore be increased by drugs that induce these enzymes and reduced by drugs that inhibit cytochrome P450. Where co-administration of such agents is necessary, the dosage of Lamisil tablets must be adjusted accordingly.
Enzyme inhibitors: a 30% reduction in terbinafine clearance and a 34% increase in the AUC have been reported in association with the combination of terbinafine with cimetidine.
Combination with fluconazole (a CYP3A4 and CYP2C9 inhibitor) increased Cmax and AUC by 52% and 69%, respectively. Similar effects may occur when other active substances which inhibit CYP2C9 and/or CYP3A4, such as azole antifungals, macrolide antibiotics or amiodarone, are concomitantly administered with terbinafine.
Enzyme inducers: combination with rifampicin, a CYP3A4 inducer, increased terbinafine clearance by 100%. AUC and Cmax were reduced by 50% and 45%, respectively.

Influence of terbinafine on the pharmacokinetics of other medicinal products
CYP2D6 substrates: in vitro and *in vivo* studies have shown that terbinafine inhibits CYP2D6. These findings might be relevant for substances that are predominantly metabolised by this enzyme, especially if they have a narrow therapeutic window (see "Warnings and precautions"). This applies, for example, to certain members of the following drug classes: tricyclic antidepressants, beta blockers, selective serotonin reuptake inhibitors, class 1A, 1B and 1C antiarrhythmics or type-B MAO inhibitors.
The clearance of desipramine decreased by 82% during concomitant administration of terbinafine and the AUC was increased 5-fold.
In rapid CYP2D6 metabolisers terbinafine increased the dextromethorphan/dextrorphan metabolic ratio in urine by 16-fold to 97-fold on average. This indicates that terbinafine slows down the metabolism of CYP2D6 substrates in rapid CYP2D6 metabolisers ("extensive metabolisers"), meaning that the metabolism in these patients more closely corresponds to that of slow metabolisers (i.e. "poor metabolisers).
Substrates of other CYP450 enzymes: according to the results of studies performed *in vitro* and in healthy volunteers the action of terbinafine in inhibiting or inducing the clearance of most drugs metabolised via other isoforms of the cytochrome P450 system (e.g. terfenadine, triazolam or oral contraceptives) is negligible.

Other metabolic pathways:
Terbinafine increased the clearance of ciclosporin by 15% (13% reduction in AUC).
The possibility of interactions between terbinafine and anticoagulants commonly prescribed in Switzerland was not investigated. No interactions were observed in a study with warfarin.
Terbinafine reduced the clearance of intravenously administered caffeine by 21%.
In clinical studies there was no relevant effect on the pharmacokinetics of cotrimoxazole (trimethoprim and sulfamethoxazole), digoxin, fluconazole, phenazone, theophylline or zidovudine.

Pregnancy/Breast-feeding

Reproductive toxicity studies in animals have shown no evidence of risk to the foetus; however, there have been no controlled studies in pregnant women. Clinical experience with Lamisil tablets in pregnant women is very limited.
Lamisil tablets should not be used during pregnancy unless clearly necessary.
Small amounts of terbinafine are excreted in breast milk (see "Pharmacokinetics"). Patients being treated with Lamisil should therefore not breast-feed.

Effects on the ability to drive and to use machines

Relevant studies have not been conducted. Adverse effects such as dizziness and visual disturbances may occur under treatment with Lamisil tablets (see "Adverse effects"), which may impair patients' ability to drive and operate machinery.

Adverse effects

The following adverse effects were observed in clinical studies and/or during the post-marketing period.

Frequencies
Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (primarily based on spontaneous post-marketing reports; precise frequency cannot be estimated).

Blood and lymphatic system disorders
Uncommon: anaemia.
Very rare: neutropenia, agranulocytosis, thrombocytopenia, pancytopenia.

Immune system disorders
Very rare: anaphylactoid reactions (including angioedema), acceleration and exacerbation of systemic and cutaneous lupus erythematosus.
Unknown: anaphylactic reactions, reactions similar to serum sickness (including rash, pruritus, urticaria, oedema, arthralgia, fever and lymph node swelling).

Metabolism and nutrition disorders
Very common: loss of appetite.
Uncommon: weight loss (secondary to dysgeusia).
There have been reports of severe isolated cases of reduced food intake leading to significant weight loss.

Psychiatric disorders
Common: depression.
Uncommon: anxiety.

Nervous system disorders
Very common: headache.
Common: dizziness, dysgeusia through to ageusia, although the sense of taste usually returns to normal following withdrawal of treatment.
Uncommon: paraesthesia, hypoaesthesia.
Very rare: persistent dysgeusia.
Unknown: hyposmia, anosmia (including permanent anosmia).

Eye disorders
Common: visual disturbance.
Unknown: blurred vision, reduced visual acuity.

Ear and labyrinth disorders
Uncommon: tinnitus.
Not known: hypoacusis.

Vascular disorders
Unknown: vasculitis.

Gastrointestinal disorders
Very common: bloated feeling, dyspepsia, nausea, mild abdominal pain, diarrhoea.
Unknown: pancreatitis.

Hepatobiliary disorders
Rare: increased hepatic enzymes, icterus, cholestasis, hepatitis, hepatic failure (including cases with a fatal outcome or requiring liver transplantation; see "Warnings and precautions").

Skin and subcutaneous tissue disorders
Very common: rash, urticaria.
Uncommon: photosensitivity.
Very rare: alopecia, psoriasiform rash or exacerbation of psoriasis, toxic skin eruption, exfoliative dermatitis, bullous dermatitis, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), acute generalised exanthematous pustulosis.
Not known: drug rash with eosinophilia and systemic symptoms.

Musculoskeletal disorders
Very common: arthralgia, myalgia.
Unknown: CK elevation, rhabdomyolysis.

General disorders and administration site conditions
Common: exhaustion.
Uncommon: fever.
Not known: influenza-like illness.

Overdose

A few cases of overdosage, involving doses up to 5 g, have been reported. Following ingestion patients complained of headache, nausea, upper abdominal pain and dizziness.
The recommended treatment of overdosage consists of eliminating the drug by administering activated charcoal and giving symptomatic supportive therapy if necessary.

Properties/Actions

ATC code: D01BA02

Mechanism of action
Terbinafine is an allylamine with a range of antifungal activity against fungal infections of the skin, hair and nails caused by dermatophytes such as Trichophyton (e.g. *T. rubrum, T. mentagrophytes, T. verrucosum, T. tonsurans, T. violaceum*), *Microsporum canis* and *Epidermophyton floccosum* and against yeast infections of the skin caused by the genus Candida (e.g. *Candida albicans*). Terbinafine is fungicidal against dermatophytes, moulds and certain dimorphic fungi. Its activity against yeasts is fungicidal or fungistatic, depending on the species.
Terbinafine interferes with fungal ergosterol biosynthesis at an early stage. It acts by inhibiting squalene epoxidase in the fungal cell membrane. This leads to a deficiency in ergosterol and to intracellular accumulation of squalene, resulting in fungal cell death.

The enzyme squalene epoxidase is not dependent on the cytochrome P450 system.

Microbiology	
Minimum inhibitory concentration *in vitro*	
Fungal species	µg/ml
Susceptible:	
Trichophyton rubrum	0.003-0.006
T. mentagrophytes	0.003-0.01
T. tonsurans	0.003
T. verrucosum	0.003
T. schönleinii	0.006
Microsporum canis	0.006-0.01
M. persicolor	0.003
M. gypseum	0.006
Epidermophyton floccosum	0.003-0.006
Moderately susceptible:	
Aspergillus fumigatus	0.1-1.56
Sporothrix schenckii	0.1-0.4
Candida albicans:	
Yeast form	25-100
Mycelium form	0.2-3.0
C. parapsilosis	0.8-3.1
P. orbiculare	0.8

In animal studies fungicidal concentrations of terbinafine were attained in the skin, hair and nails following oral dosing.

Pharmacokinetics

Absorption
Following oral administration terbinafine is well absorbed (>70%). The absolute bioavailability of terbinafine from Lamisil tablets is approximately 50% as a result of first-pass metabolism. A single oral dose of 250 mg terbinafine resulted in a peak plasma concentration of 1.3 µg/ml within 1.5 hours of administration.
Concomitant ingestion of high-fat foods delays absorption and increases bioavailability by approximately 20%.

Steady state
With daily administration of terbinafine approx. 70% steady state is achieved in 28 days. In comparison to a single dose peak concentration at steady state was on average 25% higher and plasma AUC increased by a factor of 2.3.

Distribution
Terbinafine is 99% bound to plasma proteins. It has a volume of distribution in excess of 2000 litres.
Terbinafine accumulates in the lipophilic stratum corneum of the skin. It is also excreted in sebum. High concentrations are also achieved in hair, hair follicles and sebum-rich skin. There is evidence that terbinafine is also distributed in the nail plate as early as the first few weeks of treatment.
There are no adequate data on whether terbinafine crosses the placental barrier. Less than 0.2% of the ingested dose is excreted in breast milk.

Metabolism
Terbinafine is metabolised in the liver rapidly and extensively to inactive metabolites by at least seven CYP isoenzymes, primarily CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19.

Elimination
Terbinafine metabolites are excreted in the urine (71%) and the faeces (22%).
At steady state an elimination half-life of around 30 hours was calculated. However, the literature describes triphasic elimination with half-lives of up to 16.5 days in long-term therapy.

Pharmacokinetics in special populations
No clinically relevant age-dependent changes in steady-state plasma concentrations of Lamisil have been observed.
In single-dose studies terbinafine clearance was reduced by about 50% in patients with renal impairment (creatinine clearance <50 ml/minute) or pre-existing liver disease.

Preclinical data

In a two-year oral carcinogenicity study in mice there were no neoplastic or other abnormal findings at daily doses of up to 130 mg/kg (males) and 156 mg/kg (females). In a two-year oral carcinogenicity study in rats an increased incidence of liver tumours was observed in males given the highest dose of 69 mg/kg per day. These changes, which may be associated with peroxisome proliferation, should be considered species-specific, since they were not seen in the carcinogenicity study in mice or in other studies in mice, dogs or monkeys.
During studies in monkeys given high oral doses of terbinafine retractile irregularities were observed in the retina (no-observed-effect level of 50 mg/kg). These irregularities, which were associated with the presence of terbinafine metabolites in ocular tissue, disappeared after drug discontinuation. They were not associated with histological changes.
A standard battery of *in vitro* and *in vivo* genotoxicity tests revealed no evidence of mutagenic or clastogenic potential of the medicinal product.
No adverse effects on fertility or other reproduction parameters were observed in studies in rats or rabbits.
An 8-week study in juvenile rats showed slightly increased liver weights at a maximum dose of 100 mg/kg in females, while signs of central nervous system (CNS) disturbances – including isolated episodes of convulsions in individual animals – were observed in maturing dogs given ≥100 mg/kg/day (AUC about 13× [male] and 6× [female] greater than in children). Similar findings have been observed at high systemic exposure following intravenous administration of terbinafine to adult rats or monkeys.

Other information

Special precautions for storage
Keep out of the reach of children.
Do not use after the expiry date (« EXP) printed on the pack.
Protect from light and do not store above 30°C.

Pack sizes

125 mg scored tablets (for paediatric use): packs containing 14* tablets.
250 mg scored tablets: calendar packs containing 14* or 28* tablets.
*Not All Pack sizes are marketed

Manufacturer

See folding box.

Information last revised

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® = registered trademark
Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists